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FORMULATION AND EVALUATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM OF POORLY SOLUBLE ANALGESIC

S. Chouhan

Pharmacy Wing, Lachoo Memorial College of Science and Technology (Autonomous), Shastri Nagar Jodhpur - 342003, Rajasthan, India.

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Correspondence to Author:
Ms. Shailendra Chouhan

Research Scholar, Department of Pharmaceutical Sciences, Mohan Lal Sukhadia University, Udaipur - 342003, Rajasthan, India.

E-mail: shailendra.chouhan26@gmail.com

ABSTRACT: In the present work, the aim was to prepare a self-emulsifying drug delivery system of poorly soluble analgesic, mefenamic acid to improve its solubility with a view to enhance its oral bioavailability. From the solubility studies the selected oil, surfactant and co-surfactant was soyabean oil; tween 80, span 20; glycerol. Blends of surfactant mixtures containing tween 80, span 20, and glycerol were prepared. Three ratios of S_{mix} containing tween 80: span 20: glycerol *viz.* 1:0.25:1, 1:1:1, 2:2:1; were used to construct pseudo ternary phase diagram to select nine formulation composition. Nine self-emulsifying formulations of mefenamic were prepared and evaluated for optical transparency, low refractive index, uniformity index, low viscosity, and drug release. The best formulations in all aspects of the evaluation were subjected to stability testing. The optimized formulation has been found to have good physical stability and longest shelf life of 13.45 months under accelerated storage conditions with degradation rate constant 1.38 $\times 10^{-3}$ months.

INTRODUCTION: Oral route is the most common route for delivering most of the available drugs into the bloodstream. This is the most suitable route for delivering hydrophilic drugs into the patient's body as the hydrophilic drugs get absorbed up to a considerable extent by easy diffusion through the gastrointestinal tract. As 40% of the total available drugs are lipophilic and possess low solubility in gastric fluid, it is one of the significant challenges to deliver these drugs through oral route [1]. Self-emulsifying drug delivery systems (SEDDS) are a potential tool in improving the bioavailability of low solubility drugs.

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SEDDS formulations are isotropic pre-mixtures composed of natural or synthetic oils with lipophilic or hydrophilic surfactants and co-solvents which emulsify spontaneously when exposed to fluids of the gastrointestinal tract to form oil in water emulsions or microemulsions. These systems bypass the first-pass hepatic metabolism as *in-situ* solubilized drugs can be directly absorbed through the lymphatic pathway.

Besides, all these increased drug loading capacity has been observed in SEDDS formulations as the solubility of poorly water-soluble drugs with intermediate partition coefficients (2<log P<4) are typically low in natural lipids as compared to high solubility in amphiphilic surfactants, co-surfactants and co-solvents [2, 3]. A poorly water-soluble compound is one that solubilizes less than 1 part per 10000 parts of water. A poorly water-soluble drug has been defined in general terms, which

require more time to dissolve in the gastrointestinal fluid than it takes to be absorbed in the gastrointestinal tract [4]. Mefenamic acid is a non-steroidal anti-inflammatory drug with poor water solubility and has been categorized as a BCS class II drug. It belongs to fenamates family (N-phenylantranilic acid derivative) of NSAIDs. Its IUPAC name is 2-(2, 3-dimethylphenyl) aminobenzoic acid. Its GIT absorption is limited by its dissolution in the gastrointestinal fluids exhibiting a low bioavailability after oral administration [5, 6].

Mefenamic acid is used for the relief of moderate severity in conditions such as headache, dental pain, dysmenorrhoea (drug of choice), and muscular aches [7]. Mefenamic acid has been available as capsule, tablet and suspension for more than 30 years. The bioavailability of mefenamic acid has been found to vary significantly depending on the pharmaceutical formulations. Hence, SEDDS can serve as an important tool in improving the bioavailability of mefenamic acid [8].

MATERIALS AND METHODS: Mefenamic acid was obtained as a gift sample from Swiss Medicare Private Limited, India. Soyabean oil, olive oil, castor oil, oleic acid, isopropyl myristate, octanol and propylene glycol were purchased from Ases Chemical Works, Jodhpur, India. Tween 20, Tween 80, Span 20, potassium dihydrogen phosphate and sodium hydroxide were purchased from Loba Chemie, Mumbai, India. Glycerol and Ethanol was purchased from Siphon Laboratories, Jodhpur, India. Other chemicals were of reagent or analytical grade and used without further purification. Distilled water (In House) was used in all preparations.

Solubility Determination in Various Oils, Surfactants and Co-surfactants: 2 ml of different oils, surfactants, and co-surfactants were taken in separate vials, and an excess amount of mefenamic acid was added to each vial. After continuous mixing in a mechanical shaker for 72 h at room temperature, the vehicles were subjected to centrifugation.

The supernatant was separated and dissolved in ethanol, and solubility was determined by UV Spectroscopy (Shimadzu, 1800) at 283 nm after dilution with ethanol [9].

Construction of Pseudoternary Phase Diagram: Based on solubility studies, soyabean oil as oil, Tween 80, and Span 20 as surfactants and glycerol as co-surfactant was selected for construction of pseudo ternary phase diagrams. The various ratios of oil (containing drug): S_{mix} (1, 2, 3) taken are 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 respectively as shown in **Table 1**, **Table 2** and **Table 3**.

The pseudo-ternary phase diagram of oil (containing drug), surfactants: co-surfactant and water were developed using water titration method: the mixtures of oil and surfactant / co-surfactant at certain weight ratios were diluted with water in a dropwise manner.

These diagrams were constructed to identify the self-emulsifying region and to optimize the concentration of oil. For each phase diagrams a a specific ratio of Tween 80: Span 20: glycerol, 1:0.25:1 S_{mix} 1, 1:1:1 S_{mix} 2, 2:2:1 S_{mix} 3 (v/v/v) were prepared.

A homogenous mixture of oil containing drug and S_{mix} (1, 2, 3) was formed under the mixing by magnetic stirring. The various ratios of oil (containing drug): S_{mix} (1, 2, 3) were taken; 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 and pseudo ternary diagrams were constructed [9].

TABLE 1: VARIOUS COMPOSITIONS FOR THE CONSTRUCTION OF PSEUDOTERNARY PHASE DIAGRAM USING S_{MIX} 1

S. no.	Oil: S_{mix} blend (v/v)	Volume of oil (%)	Volume of S_{mix} (%)	Volume of water (%)
1	1:9	7.04	63.3	29.57
2	2:8	15.26	61.06	23.66
3	3:7	23.80	55.55	20.63
4	4:6	37.38	56.07	6.54
5	5:5	47.16	47.16	5.66
6	6:4	57.14	38.09	4.76
7	7:3	67.3	28.84	3.84
8	8:2	77.66	19.41	2.91
9	9:1	88.23	9.80	1.96

TABLE 2: VARIOUS COMPOSITIONS FOR THE CONSTRUCTION OF PSEUDOTERNARY PHASE DIAGRAM USING S_{MIX} 2

S. no.	Oil: S_{mix} blend (v/v)	Volume of oil (%)	Volume of S_{mix} (%)	Volume of water (%)
1.	1:9	6.06	54.54	39.39
2.	2:8	13.33	53.33	33.33
3.	3:7	21.58	50.35	28.05
4.	4:6	30.76	46.15	23.07
5.	5:5	41.66	41.66	16.66
6.	6:4	53.57	35.71	10.71
7.	7:3	65.42	28.03	6.54
8.	8:2	76.19	19.04	4.76
9.	9:1	88.23	9.80	1.96

TABLE 3: VARIOUS COMPOSITIONS FOR THE CONSTRUCTION OF PSEUDOTERNARY PHASE DIAGRAM USING S_{MIX} 3

S. no.	Oil: S_{mix} blend v/v	Volume of oil (%)	Volume of S_{mix} (%)	Volume of water (%)
1.	1:9	6.75	60.81	32.43
2.	2:8	14.08	56.33	29.57
3.	3:7	22.22	51.85	26.66
4.	4:6	29.85	44.77	26.11
5.	5:5	37.50	37.50	24.81
6.	6:4	46.87	31.25	21.87
7.	7:3	55.55	23.80	20.63
8.	8:2	65.57	16.39	18.03
9.	9:1	75.63	8.40	15.96

Rheology: The viscosity of the formulated batches was determined using a Brookfield viscometer (small sample adapter assembly) with spindle SC4-27. The formulations were added one by one to the sample adapter at room temperature, and then the measurements were taken.

Droplet Size Analysis: 1 ml of each of the formulations were diluted with 100 ml of water in a volumetric flask and shaken till it gets completely dispersed. The globules of the prepared formulations were observed under Olympus SZX 16 stereo zoom microscope, and the size of globules was determined.

Uniformity Index: Uniformity index is calculated in order to determine whether the prepared emulsion is monodispersed or polydispersed. It is the ratio of average weight diameter to average number diameter.

Uniformity Index = Average weight diameter (D_w) / Average number diameter (D_n)

Where,

$$D_w = \Sigma n_i d_i^{\,4} / \Sigma n_i d_i^{\,3} \text{ and } D_n = \Sigma n_i d_i / \Sigma n_i$$

d_i = mean diameter of particles; n_i = number of particles with diameter d_i

If uniformity index is one then sample is monodispersed.

Phase Separation: Phase separation is an indication of the stability of the emulsion. It is determined by the centrifugation and by subjecting the diluted formulations to a freeze-thaw cycle.

Centrifugation: The prepared mefenamic acid pre-concentrates were diluted (1 ml in 100 ml) of water and then subjected to centrifugation at 3000 rpm for 30 min and observed visually for phase separation.

Freeze-thaw Cycle: The prepared were mefenamic acid pre-concentrates were diluted (1 ml in 100 ml) of water and then kept at a temperature between 0-8 °C and then allowed to melt at room temperature. This cycle is repeated three times [10].

Drug Content: 5 ml of the prepared formulations were dissolved separately in 25 ml of ethanol in a 100 ml volumetric flask, and volume was made up to 100 ml by ethanol. The mixture is shaken well for 15-20 min and kept for 24 h. The solution was filtered through 0.45 µm filter paper. The filtrate was assayed spectro-photometrically at 284 nm using a UV-Visible spectrophotometer.

***In-vitro* Dissolution Study:** The release of mefenamic acid from the prepared formulations was determined by using USP-II dissolution apparatus at 30 rpm and using phosphate buffer pH 6.8 as dissolution medium at 37 ± 0.5 °C. The

release of the drug at various time intervals was determined by the aid of UV-Visible spectroscopy.

The release pattern of the drug from the self-emulsifying formulations was compared to crude drug and marketed suspension purchased from a retail pharmacy in India [9].

RESULTS AND DISCUSSION:

Pseudo Ternary Phase Diagram Study: The pseudo ternary phase diagram of the system comprising the oily phase containing drug and S_{mix} 1, S_{mix} 2 and S_{mix} 3 are shown in **Fig. 1**, **2,** and **3** respectively. Area enclosed within the solid line represents the region of self-emulsification.

On the basis of pseudo ternary phase diagram study formulas have been derived from the self-emulsifying area of the pseudo ternary diagram for the three ratios of S_{mix} and nine different formulations composed of S_{mix} 1 (F1, F2, F3), S_{mix} 2 (F4, F5, F6) and S_{mix} 3 (F7, F8, F9) which shows maximum transparency, homogeneity based on visual observations are considered for further, evaluation.

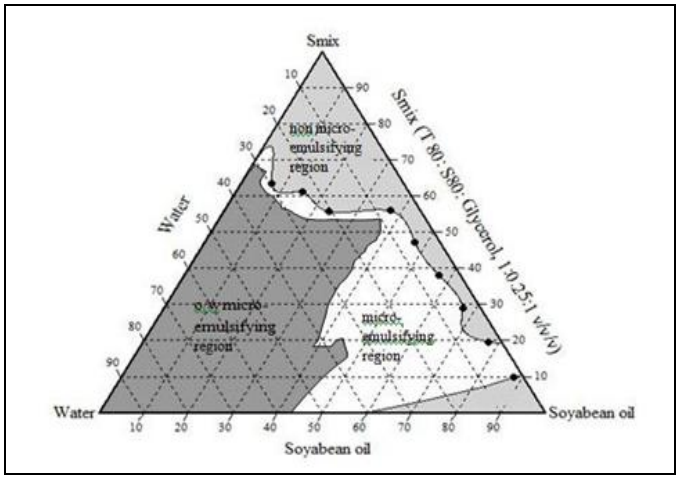

FIG. 1: PSEUDOTERNARY PHASE DIAGRAM FOR WATER: SOYABEAN OIL CONTAINING MEFENAMIC ACID: S_{MIX} 1

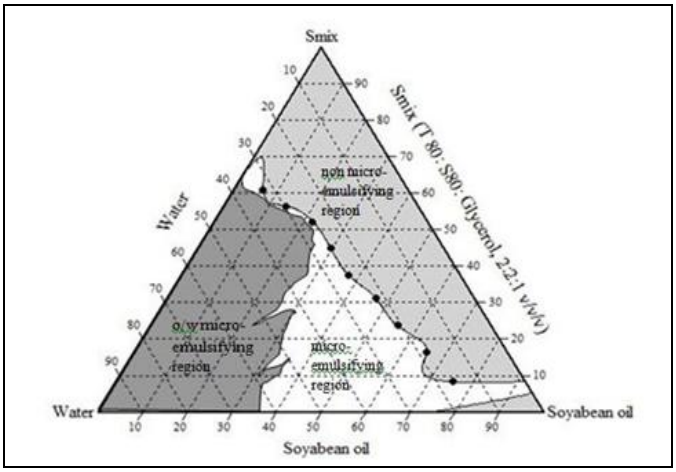

FIG. 2: PSEUDOTERNARY PHASE DIAGRAM FOR WATER: SOYABEAN OIL CONTAINING MEFENAMIC ACID: S_{MIX} 2

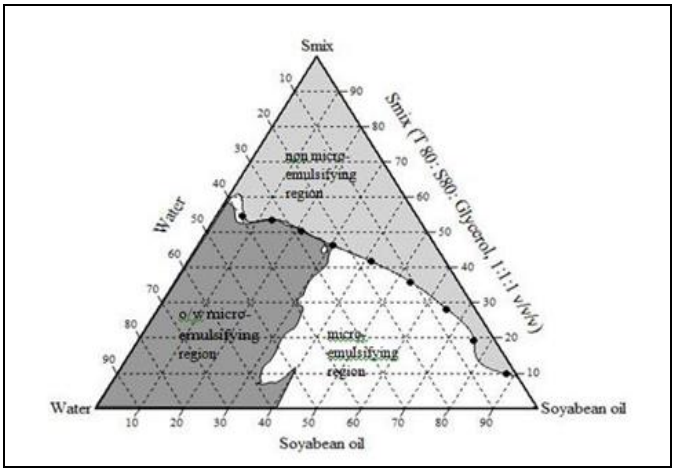

FIG. 3: PSEUDOTERNARY PHASE DIAGRAM FOR WATER: SOYABEAN OIL CONTAINING MEFENAMIC ACID: S_{MIX} 3

Homogeneity: The prepared SEDDS precon-centrates were inspected visually for their colour and homogeneity. The prepared SEDDS pre-concentrates were viscous, preparations, with an oily and homogenous appearance.

pH Determination: The pH of the prepared SEDDS pre-concentrates was determined by using a digital pH meter. The test was performed in triplicate using a digital pH meter and the mean was calculated.

The pH of all the pre-concentrates was found to be in the range of 7.1 to 7.4, which lies in the normal pH range of the physiological fluids.

Optical Transparency: The optical transparency of the SEDDS formulations was determined by using nepeheloturbidimeter at NTU 1000. The readings were taken in triplicate, and the average was calculated. The maximum transmittance found to be 99 ± 1 for formulation F3.

Rheology: Determined viscosity for prepared SEDDS is represented in **Table 4**. It has been found that as rpm is increased, viscosity decreases. At 50, 60, 100 rpm the viscosity follows the order: F1<F2<F3<F4<F5<F6<F7<F8<F9.

The reason which can be attributed to the above observations can be attributed to the following fact is as the surfactant blend (Tween 80, Span 80, glycerol) proportion, in oil: S_{mix} mixture increases, viscosity increases significantly ($p<0.05$) as shown in **Fig. 4**, **Fig. 5,** and **Fig. 6**.

TABLE 4: VISCOSITY OF MEFENAMIC ACID SEDDS

Rpm	Viscosity ± Standard deviation (cps)		
	50	60	100
F1	163.8 ± 3	122.4 ± 3	105.0 ± 3
F2	164.8 ± 3	123.3 ± 3	106.7 ± 3
F3	167.8 ± 3	128.2 ± 3	109.0 ± 3
F4	175.6 ± 2	130.4 ± 3	113.7 ± 2
F5	177.4 ± 2	134.2 ± 3	117.8 ± 3
F6	181.2 ± 3	137.4 ± 3	119.3 ± 3
F7	204.3 ± 3	144.0 ± 2	123.8 ± 3
F8	206.0 ± 2	147.0 ± 3	125.0 ± 3
F9	208.2 ± 3	149.5 ± 3	129.3 ± 2

Rpm is rotation per minute, cps is centipoises

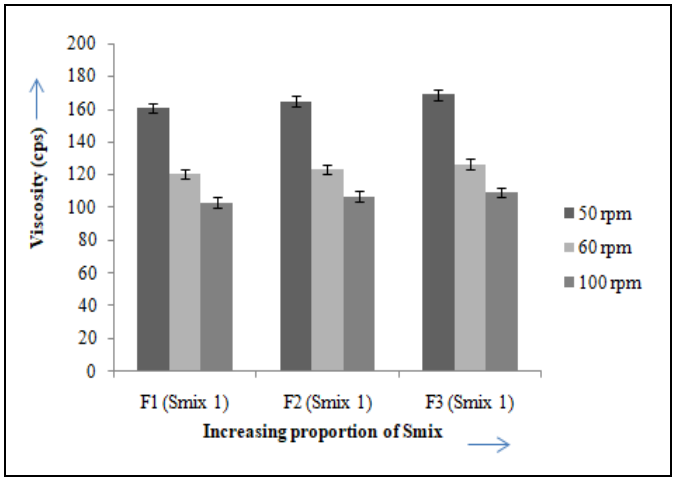

FIG. 4: EFFECT OF INCREASING PROPORTION OF SMIX 1 IN OIL: S_{MIX} BLEND ON VISCOSITY

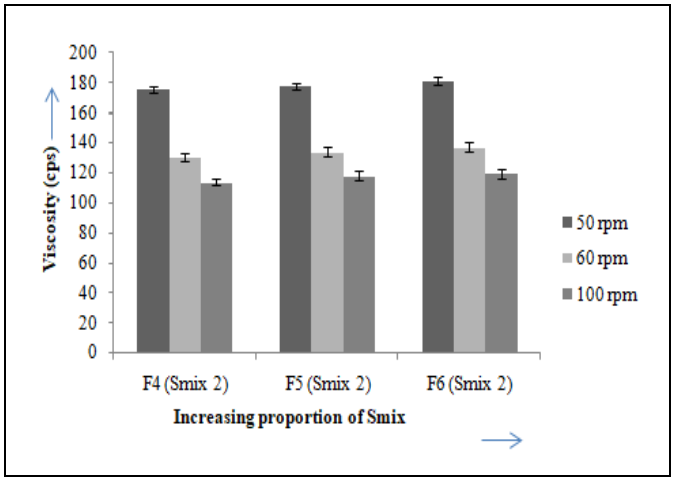

FIG. 5: EFFECT OF INCREASING PROPORTION OF SMIX 2 IN OIL: S_{MIX} BLEND ON VISCOSITY

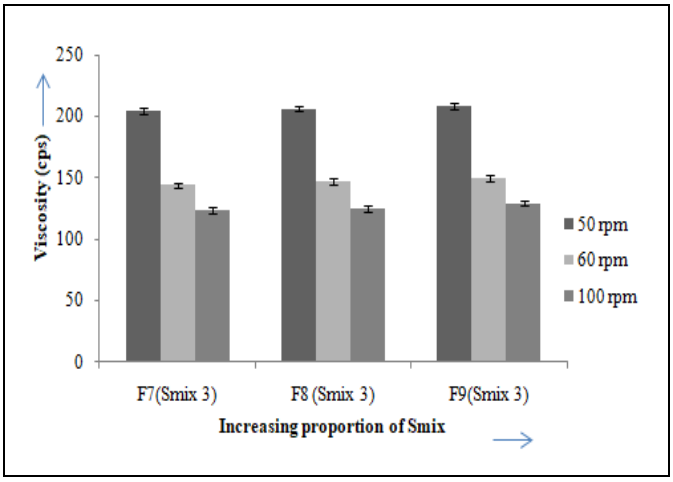

FIG. 6: EFFECT OF INCREASING PROPORTION OF SMIX 3 IN OIL: S_{MIX} BLEND ON VISCOSITY

Refractive Index: Refractive indices of the prepared formulations (pre-concentrates) were determined by the aid of Abbe's refract meter to determine the isotropic of prepared formulations. The refractive index of water was measured with the same as standard for comparison, which was found to be 1.330. The refractive indices of the prepared formulations F1-F9 range between 1.302-

1.315, which shows that the formulations are isotropic, as shown in **Table 5**.

TABLE 5: REFRACTIVE INDEX OF MEFENAMIC ACID SEDDS

S. no.	Formulation code	Refractive Index
1.	F1	1.302
2.	F2	1.302
3.	F3	1.302
4.	F4	1.307
5.	F5	1.308
6.	F6	1.307
7.	F7	1.315
8.	F8	1.313
9.	F9	1.312

Droplet Size Analysis: The optical micrograph of an optimized formulation is presented in **Fig. 7**. The mean globule size of the formulations was calculated, as shown in **Table 6**.

TABLE 6: MEAN GLOBULE SIZE OF PREPARED FORMULATIONS

S. no.	Formulation code	Mean globule size (µm*) = Σnd/Σn
1.	F1	0.250
2.	F2	0.250
3.	F3	0.250
4.	F4	0.250
5.	F5	0.253
6.	F6	0.253
7.	F7	0.256
8.	F8	0.259
9.	F9	0.259

µm is micro-meter

It was found that a slight difference in globule size (ranging from 0.250-0.259) was observed depending upon the formulation composition and ratio of S_{mix}.

The formulation of S_{mix} 1 (F1-F3) was found to contain the smallest mean globule size, whereas there is a slight increase in mean globule size of formulations of S_{mix} 2 and S_{mix} 3.

Also, the globule size of Smix 3 formulations is largest. These observations suggest that S_{mix} 1 is the optimum ratio among all the S_{mix} ratios; further, increases in surfactants proportion as in the case of S_{mix} 2 and S_{mix} 3, the globule size increases slightly, which might be due to attainment of critical micelle concentration (CMC).

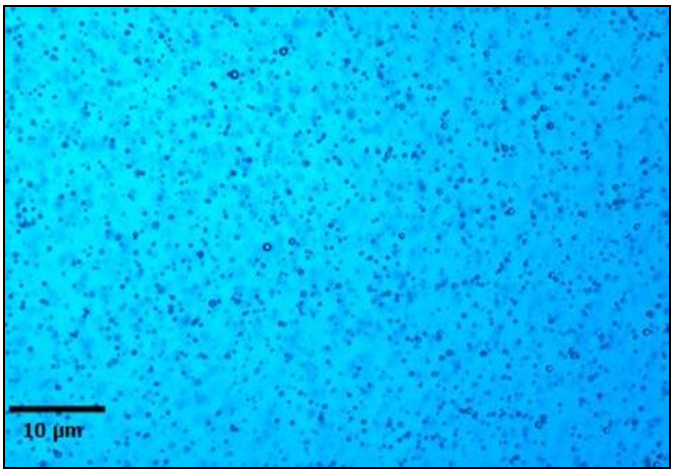

FIG. 7: OPTICAL MICROGRAPH OF OPTIMIZED FORMULATION OF MEFENAMIC ACID SEDDS

Uniformity Index: The observations for uniformity index are shown in **Table 7**. It has been found that formulations F1, F2, F3, F4 have uniformity index close to one.

Phase Separation: After subjecting the formulations to centrifugation and freeze-thaw cycles, it has been observed visually that no formulation showed the signs of phase separation.

Drug Content: The drug content was then calculated, as shown in **Table 8**.

It has been found that one of the formulations has drug content of greater than 99%, while all the formulations have drug content above 94%.

TABLE 7: OBSERVATIONS FOR UNIFORMITY INDEX

Formulation code	Average weight diameter $D_w=\Sigma n_i d_i^4/\Sigma n_i d_i^3$	Average number diameter $D_n=\Sigma n_i d_i/\Sigma n_i$	Uniformity index D_w/D_n
F1	0.251	0.250	1.004
F2	0.249	0.250	0.996
F3	0.247	0.250	0.988
F4	0.252	0.250	1.008
F5	0.565	0.253	2.233
F6	0.566	0.253	2.237
F7	0.566	0.254	2.230
F8	0.752	0.255	2.950
F9	0.751	0.255	2.945

TABLE 8: DRUG CONTENT OF THE PREPARED MEFENAMIC ACID SEDDS

S. no.	Formulation code	Drug content
1	F1	97.33 ± 0.63
2	F2	98.42 ± 0.52
3	F3	99.15 ± 0.34
4	F4	97.32 ± 0.28
5	F5	96.51 ± 0.45
6	F6	97.14 ± 0.62
7	F7	95.12 ± 0.48
8	F8	95.31 ± 0.29
9	F9	94.10 ± 0.28

TABLE 9: *IN-VITRO* RELEASE OF MEFENAMIC ACID FROM PREPARED SEDDS PRE-CONCENTRATES

Time (minutes)	% Cumulative drug release*				
Formulation code	5	15	30	45	60
F1	21.60 ± 0.2	32.40 ± 0.6	71.60 ± 0.5	76.50 ± 0.5	94.60 ± 0.3
F2	21.60 ± 0.3	33.30 ± 0.4	75.60 ± 0.4	83.70 ± 0.5	94.50 ± 0.4
F3	24.30 ± 0.3	36.90 ± 0.4	78.30 ± 0.3	84.60 ± 0.5	96.90 ± 0.4
F4	19.80 ± 0.3	28.30 ± 0.3	68.80 ± 0.3	79.20 ± 0.4	89.10 ± 0.4
F5	20.90 ± 0.4	32.90 ± 0.4	76.00 ± 0.4	84.10 ± 0.3	94.50 ± 0.3
F6	21.60 ± 0.2	32.40 ± 0.4	70.50 ± 0.5	76.50 ± 0.4	93.60 ± 0.5
F7	17.00 ± 0.5	26.50 ± 0.4	64.70 ± 0.4	72.60 ± 0.3	86.20 ± 0.4
F8	15.80 ± 0.4	24.60 ± 0.3	52.80 ± 0.4	66.90 ± 0.3	79.20 ± 0.5
F9	12.20 ± 0.3	22.10 ± 0.3	44.70 ± 0.4	56.20 ± 0.3	68.20 ± 0.4
Plain mefenamic acid	16.20 ± 0.4	26.10 ± 0.4	34.20 ± 0.6	41.40 ± 0.4	47.40 ± 0.3
Marketed suspension	22.50 ± 0.4	34.20 ± 0.3	73.10 ± 0.3	81.90 ± 0.4	96.80 ± 0.3

* Data indicate mean ± SD for n = 3 observations

***In-vitro* Dissolution Study:** The release of mefenamic acid from the prepared formulations was determined by using USP-II dissolution apparatus at 30 rpm and using phosphate buffer pH 6.8 as dissolution medium.

The release of the drug at various time intervals was determined by the aid of UV-Visible spectroscopy, as shown in **Table 9**. Graphically the release pattern of the drug from formulated self-emulsifying formulations as compared to plain mefenamic acid (crude drug) and the marketed suspension is shown in **Fig. 8**.

The present study clearly indicated that improvement of the dissolution rate and hence bioavailability of a poorly soluble drugs like mefenamic acid could be achieved by formulating self-emulsifying drug delivery system.

Stability Testing: The optimized formulation was selected on the basis of optical transparency, low refractive index, uniformity index, low viscosity, and drug release.

The optimized formulation was then subjected to stability studies and found to have a shelf life of 13.45 months under accelerated storage conditions as per ICH guidelines with degradation rate constant 1.38×10^{-3} $month^{-1}$.

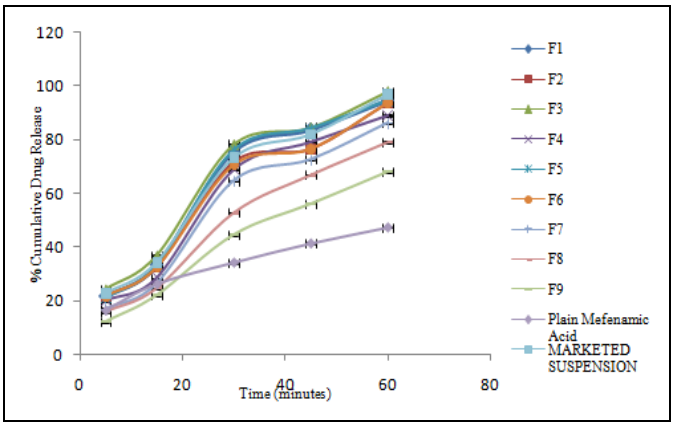

FIG. 8: RELEASE PATTERN OF MEFENAMIC ACID SEDDS WITH TIME AS COMPARED TO PLAIN DRUG AND MARKETED SUSPENSION

CONCLUSION: In the present study, the aim was to prepare self-emulsifying drug delivery system of mefenamic acid to improve its solubility with a view to enhance oral bioavailability. Nine self-emulsifying formulations were prepared and evaluated from three different ratios of surfactant mixtures containing Tween 80, Span 20, and glycerol. Out of these formulations, formulation, F3 was found to best based on globule size, optical transparency, low refractive index, low viscosity, and drug release. Also, it has been found that the drug release from formulation F3 is quite higher than plain mefenamic acid.

The optimized formulation is then subjected to stability studies and found to have a shelf life of 13.45 months under accelerated storage conditions as per ICH guidelines with degradation rate constant 1.38×10^{-3} $month^{-1}$.

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CONFLICTS OF INTEREST: The author declares there are no conflicts of interest regarding this study.

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